

For our Environment

Umwelt 
Bundesamt

noPills – Final Conference May 27-28 2015

Possible options for marketing authorisation of pharmaceutical substances

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Section IV 2.2 : Pharmaceuticals, Washing- and Cleansing Agents

**Background–
Environmental Risk Assessment in the
authorisation process of
Human Medicinal Products**

Legislation



Directive 2001/83/EC (as amended) on the Community Code relating to Medicinal Products for Human use

To characterise the potential risk of pharmaceuticals comprehensive data before marketing is needed

Recital (18)

*The environmental impact should be assessed and, on a case-by-case basis, specific arrangements to limit it should be envisaged. **In any event this impact should not constitute a criterion for refusal of a marketing authorisation.***

Article 1 (28) - Definitions

Risks related to use of the medicinal product:

- any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health;
- any risk of undesirable effects on the environment.

Article 8 3 (ca) - Marketing authorisation

Evaluation of the potential environmental risks posed by the medicinal product. This impact shall be assessed and, on a case-by-case basis, specific arrangements to limit it shall be envisaged.

Guideline



Guideline on the environmental risk assessment of medicinal products for human use

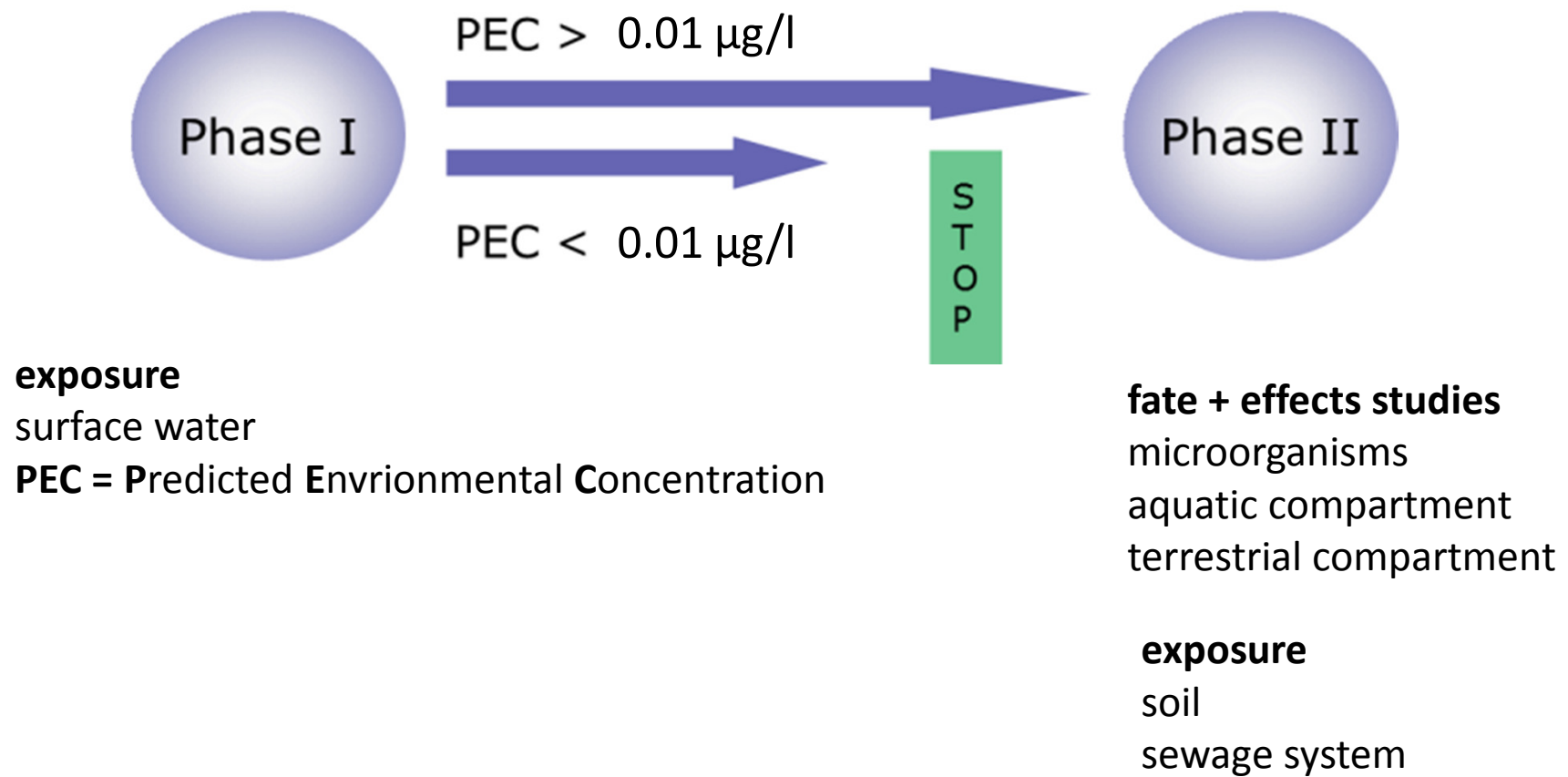
EMA/CHMP/SWP/4447/00 corr 2* (2006)

Q+A Document

Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use'

EMA/CHMP/SWP/44609/2010

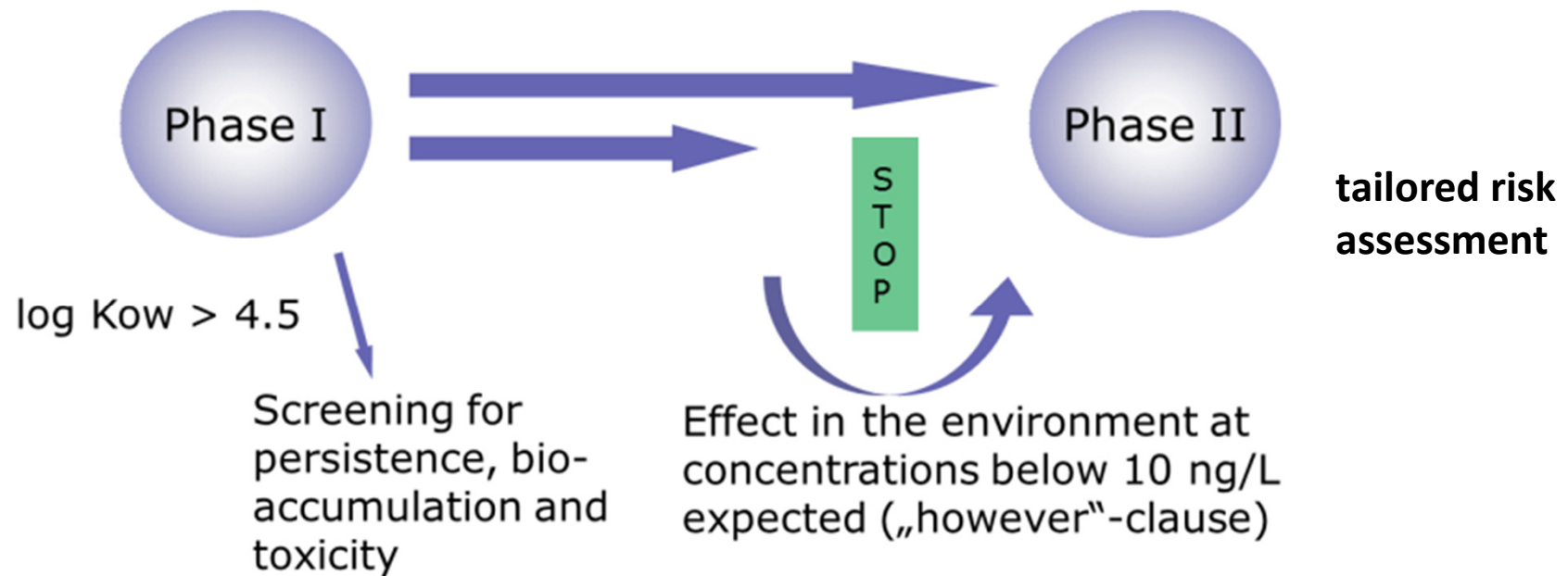
General ERA Framework for pharmaceuticals - Risk based approach



General ERA Framework for pharmaceuticals – Hazard based approach

PBT (Persistence, Bioaccumulation, Toxicity) assessment is performed regardless of action limit

Action limit not applicable for some compounds, e.g. hormones





ERA consequences

In case the active substance of the human medicinal product is

- assessed to be a hazardous substance
- assessed to pose a risk to the environment

No refusal of the product is possible !

Communication in the Summary of Product Characteristics (SmPC) and Package Leaflet (PL)

ERA category	SmPC 5.3	PL (5)
<p>No significant risk to the environment</p> <p>or</p> <p>Current ERA data do not suggest a potential risk to the environment</p>	No statement	Do not throw away any medicines via wastewater <or household waste>. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.
<p>ERA has identified a potential risk to the environment</p>	<p><i>Information to be driven by conclusion of the assessment e.g.:</i></p> <p><Environmental risk assessment studies have shown that <act.subst> has the potential to be persistent, bioaccumulative and toxic to the environment.></p> <p>or</p> <p><Environmental risk assessment studies have shown that <act.subst> may pose a risk for <environmental compartment(s)>.></p> <p>(See section 6.6)</p>	Do not throw away any medicines via wastewater <or household waste>. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

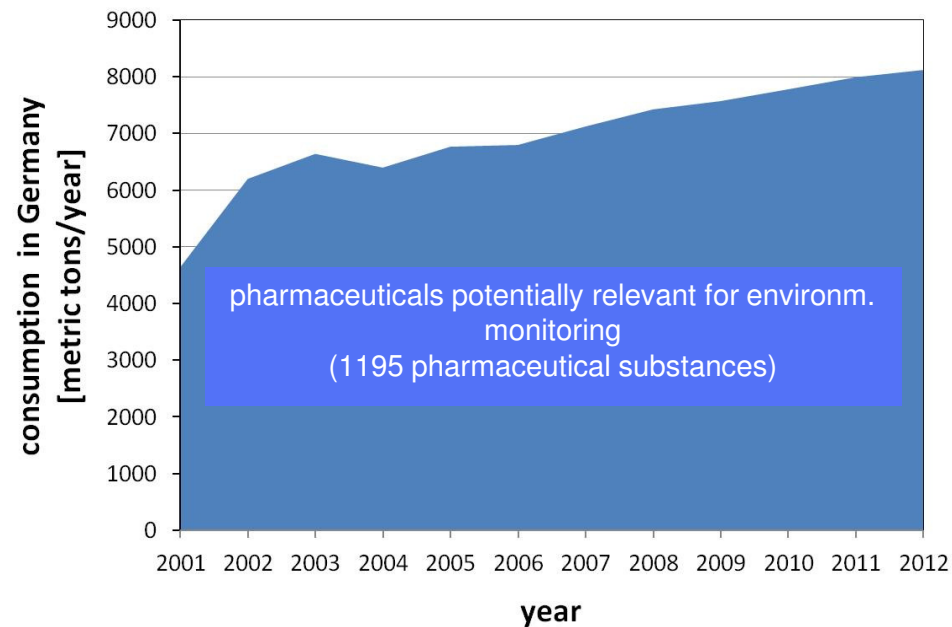
**UBA experiences –
Environmental Risk Assessment
Human Medicinal Products**

Assessment numbers (UBA)

- Audit of **about 650 ERAs** (2008-2014)
- about 200 active pharmaceutical ingredients with full dossier

The image shows a document header from the UBA (Umweltbundesamt) with the title 'Ermittlung der für die Umwelt relevanten pharmazeutischen Wirkstoffe' (Identification of environmentally relevant pharmaceutical active ingredients). It includes a table with columns for 'Wirkstoffname' (Active ingredient name), 'ATC-Code' (ATC code), 'Menge in Deutschland' (Quantity in Germany), and 'Umweltrelevanz' (Environmental relevance). The table lists various pharmaceutical substances and their quantities.

But:
In 2012 about 1200 pharmaceutical substances were identified to be potentially relevant for an environmental monitoring and their consumption increases in Germany over the last years (40%)



Pharmaceuticals (HMPs) with identified environmental risk

Risk has been identified of a variety of groups of pharmaceuticals:

- **Hormones** (e.g. ethinylestradiol)
- **Analgesics** (e.g. diclofenac, ibuprofen)
- **Antineoplastic** – also PBT (e.g. sorafenib)
- **Antidepressants** (e.g. duloxetine)

Consequence: Communication in SPC, standardised disposal information

„e.g. 5.3: Environmental Risk Assessment studies have shown that sorafenib tynsolate has the potential to be persistent, bioaccumulative and toxic to the environment. Environmental Risk Assessment information is available in the EPAR of this medicine (see section 6.6).

6.6: This medicinal product could have potential risks for the environment.“

UBA experiences- summary

- ERA of pharmaceuticals according to European guidelines is well established and is able to identify “substances of concern”
- refusal of marketing authorisation not possible due to environmental risk because environmental risks are not part of the benefit-risk-analysis
- environmental risks posed by the use of a HMP are not further considered, e.g. post marketing measures – are being communicated only in SmPC, PL

Need for action

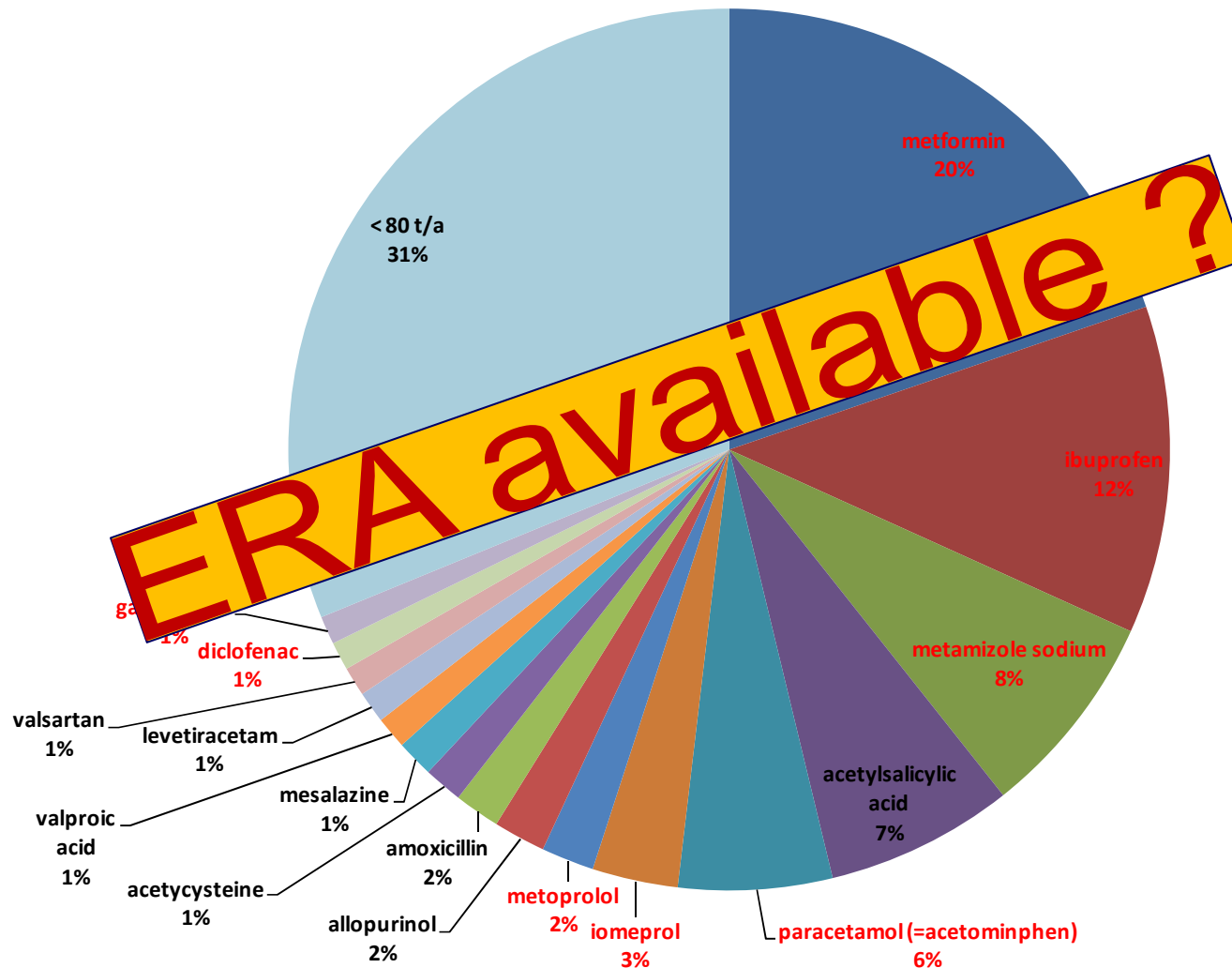
- **Include ERA results in the benefit-risk analysis for HMPs**
- **Improve risk management options**

UBA experiences – market-, monitoring data, and harmonisation

Possible options for marketing authorisation of pharmaceutical substances

Market data , monitoring data and ERA data

Top selling pharmaceuticals + also found in surface water > 0.1 µg/L



Data source: HMPs in use in Germany in 2014: DIMDI
Consumption in Germany in 2012: IMS MIDAS®

ERA data, market data and monitoring data – summary

- “old substances” – products never environmentally assessed because they came on the market before the ERA guideline came into force –
- several of these “old substances” can be measured in water bodies in amounts $> 0.1 \mu\text{g/l}$
=> but no link to Water Framework Directive is given

Need for action

- **Close data gaps for “old” substances**
- **Implement a system that pools existing data and generates missing data in high quality – „Monograph system“**
- **Establish a database for environmental data for the public**
- **Include a direct reference in WFD to ERA carried out under the EU legislation**

**Options discussed in literature -
improvement for marketing authorisation of
pharmaceutical substances**

Possible options for marketing authorisation of pharmaceutical substances

Review article: Pharmaceuticals in the environment: scientific evidence of risks and its regulation

Anette Küster, Nicole Adler

Phil. Trans. R. Soc. B 2014 369 20130587 October 2014



The regulatory ERA framework could be improved by:

- inclusion of the environment in the risk–benefit analysis for human pharmaceuticals,
- improvement of risk management options,
- generation of data on existing pharmaceuticals, and
- improving the availability of ERA data

Report: Study on the environmental risks of medicinal products Bio Intelligence Service

Final Report (2013)



- Including ERA results in the benefit-risk analysis (applying precautionary principles)
- Developing a monograph system
- Requiring agencies to communicate ERA results and data to water authorities and other interested parties
- Including a direct reference in Water Framework Directive to ERA
- Including active pharmaceutical substances as a group in WFD Annex VIII
- ...

Improving Environmental Risk Assessment of Human Pharmaceuticals

Marlene Ågerstrand et al.

Environ. Sci. Technol., 2015, 49 (9), pp 5336–5345

- Include environmental risks in the benefit-risk analysis
- Require environmental risk assessment also for product put on the market before 2006
- Perform only one environmental risk assessment per active pharmaceutical ingredient
- Increase transparency
- ...



SUMMARY

Experiences and reports from several European Member States show that legislation regarding the Environmental Risk Assessment should be improved

The following points for improvement are mentioned by several authors:

- include the ERA in the benefit-risk analysis -
 - to improve the possibilities for risk management and guarantee post marketing control
- improve transparency regarding ERA data for national water agencies and the public
 - to help identify substances of concern and provide information
- create a monograph system
 - to improve the harmonisation of assessments and the data availability for “old substances”
- link the WFD with the EU legislation on medicinal products
 - to guarantee a better prioritisation of human pharmaceuticals for monitoring programs and to improve EQS dossiers

Conclusions

- ✓ **The Environmental Risk Assessment is a well established tool before authorisation and identifies „substances of concern“.**

- ✓ **Several measures for an improved legislation were identified and in accordance with e.g. scientific findings.**

- ✓ **These measures need to be implemented as soon as possible into legislation, because...**

... this prospective approach plays an important role in minimizing entry of pharmaceuticals into surface waters at an early stage of their life-cycle!

Thank you for your attention

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Thanks to my colleagues